Remarks

Applicants submit the following amendments and remarks as submission with a Request for Continuing Examination submitted herewith in response to the final office action mailed on June 2, 2005, setting a period for response expiring September 2, 2005. Accordingly, this response is timely filed.

Claims 20-23 are pending in this application. Claim 21 was amended to read on a mixture of the tri- and hexahydrates of the disodium salt of fosfluconazole. New claim 24 was added. New claim 24 is a product by process claim which finds support throughout the specification as filed, such as in original claim 1 and page 3, line 36, to page 4, line 19. No new matter was introduced by these amendments.

Applicants' attorney, Elsa Djuardi, called supervisor Examiner Gupta because the attorney could not get in touch with Examiner Hamlin. Examiner Gupta told the attorney that Examiner Hamlin no longer works at the USPTO and that the case is now assigned to Examiner Necholus Ogden. Examiner Ogden called the attorney on September 1st 2005 and therefore this RCE is submitted to Examiner Ogden. As discussed on the same telephone call, Applicants' attorney will call Examiner Ogden to discuss the present case in or after November 2005.

Reconsideration is respectfully requested.

Rejection under 35 USC §103(a)

Claim 20 stands rejected under 35 U.S.C. § 103(a) as being obvious over the teaching of WO 97/28169. Examiner Hamlin (hereinafter "the Examiner") states that the reference teaches disodium salt of fosfluconazole (WO 97/28169, page 10, example 2). [But] The reference does not teach the instant invention with sufficient specificity to constitute anticipation. The reference fails to teach the specific hydrate. The Examiner further argued that there would be a reasonable expectation of success to modify the prior art to arrive at the instantly claimed invention because the prior art teaches disodium salt of fosfluconazole, which one of the ordinary skill in the art would reasonably expect to form the instantly claimed hydrates when put in water. The Examiner further argued that the reference discloses the claimed invention except for the exact water content of the disodium salt of fosfluconazole; that an aqueous composition would encompass 11-20 water; that it would have been obvious to those skilled in the art to use an aqueous composition with the instantly claimed antifungal materials, since it has been held that discovering an optimum of a result effective variable involves only routing skill in the art (the Examiner cited Boesch F.2d 272, 205 USPQ 215).

Applicants respectfully disagree. WO 97/28169 does not teach or suggest hydrated disodium salt of fosfluconazole (hereafter referred to as DSFF). More importantly, WO 97/28169 does not teach or suggest that DSFF exhibits plurality of hydration forms, let alone which forms are stable. Based on the reasonings below, Applicants submit that WO 97/28169 does not render the present claims obvious.

Plurality of hydration forms

Applicants respectfully submit that the present claims are directed to a stable hydrate of DSFF, more specifically a stable hydrate of a disodium salt of fosfluconazole in the form of its trihydrate, its hexahydrate, or mixtures thereof. The present inventors are the first to find that DSFF exhibits a plurality,

i.e., four, of hydrate forms. While sodium salts may generally form hydrates, it is unusual that such salts have a multiplicity of hydrate states. Quite unexpectedly, DSFF has four different hydrate forms, each having its own level of stability, as discussed below.

Water content and Hydrate stability

The stability of hydrates is unpredictable. Among the different hydrate forms of DSFF, the present inventors found that only two of them are stable, i.e. the trihydrate and the hexahydrate. Further, the present inventors found that any composition comprising an unstable hydrate form of DSFF, despite possibly containing stable forms, will decompose.

In particular, the present inventors found that hydrates of DSFF having water content below the trihydrate stoichiometry (about 11% w/w) or above the hexahydrate stoichiometry (about 20% w/w) exhibit thermal and/or chemical instability. Thus, only the trihydrate and the hexahydrate forms of DSFF are stable. Also stable are hydrate mixes having a water content of from about 11% w/w to about 20% w/w. For example, at water content of above about 20% w/w, DSFF exists as a mixture of hexahydrate (stable) and dodecahydrate (unstable). At water content of below about 11% w/w, the product will exist as a mixture of trihydrate (stable) and monohydrate (unstable). The fact that only those hydrate forms of DSFF (and mixtures thereof) having water content from about 11% w/w to about 20% w/w are stable, could not have been predicted by one skilled in the art. Indeed, since the tri and hexahydrate forms of DSFF were not known in the art, one skilled in the art could not have expected said hydrates to be stable.

The present claims reflect the property of the hydrates required for stability.

The present inventors have found a novel process for controlling the hydrate mix of a compound, e.g. DSFF. Through the process of the current invention, a compound which is found or known to have a plurality of hydration forms of differing stability can be treated to provide a hydrate mix which is both chemically and thermally stable.

The process of the invention is a multi-step process that is neither taught nor suggested by WO 97/28169. The present invention provides a process for the preparation of a stable hydrate mix of a compound, e.g. DSFF, or a composition comprising the compound, the compound being capable of forming a plurality of hydration forms of differing stability and of dissolution to give a solution that, when frozen below the eutectic point, is a eutectic mixture, comprising:

a) providing a quantity of an aqueous mixture containing the compound or composition thereof in a suitable vessel in a freeze-drying apparatus;

b) reducing the temperature in the apparatus to bring about freezing and eutectic solidification;

c) reducing the pressure in the apparatus to below the saturation vapour pressure (SVP) of water over ice at the temperature of the ice;

d) maintaining the apparatus at a pressure below the SVP and, optionally, increasing the temperature in the apparatus to facilitate sublimation, until all of the ice has been sublimed;

e) maintaining the apparatus at the pressure and temperature conditions according to step d) until the desired water content has been obtained; and

f) either:

increasing the pressure in the apparatus to from about 60% to about 100% of atmospheric pressure (about 60.8 kPa to about 101.3 kPa) and subsequently adjusting the temperature in the apparatus to from about 5°C to about 30°C;

or

adjusting the temperature in the apparatus to from about 5°C to about 30°C and subsequently increasing the pressure in the apparatus to from about 60% to about 100% of atmospheric pressure (about 60.8 kPa to about 101.3 kPa).

The above process makes it possible to control the hydrate mix of a compound, e.g. DSFF, to form a corresponding hydrate mix which is both chemically and thermally stable and can be prepared in a reproducibly facile and economically viable manner.

Based on the above discussion, the present applicants have herein added new claim 24, which is a product by process claim directed to the mix of the trihydrate and hexahydrate of disodium salt of fosfluconazole produced by the process of the invention.

Thus, contrary to the Examiner's objection, based on the teaching of WO 97/28169 and without the knowledge of the process of the present invention, those skilled in the art cannot obtain stable hydrate forms of DSFF as presently claimed. As the Examiner can see, the above multi-step process involves a lot more than just putting the disodium salt of fosfluconazole in water. Thus the Examiner's contention that those skilled in the art would arrive at the presently claimed stable mix of hydrates of disodium salt of fosfluconazole just by putting the salt in water is merely based on hindsight.

In view of the above remarks, Applicants respectfully assert that the Examiner's obviousness rejection has been overcome, and request withdrawal of the outstanding rejection. Early allowance of claims 20-24 is requested.

Respectfully submitted,

Date: Sept 2 '2005

Elsa Djuardi, Ph.D.
Attorney for Applicants
Reg. No. 45,963

Pfizer Inc.
Patent Dept.
10777 Science Center Drive
San Diego, CA 92121
Tel: (858) 638-6117
Fax: (858) 678-8233